Comments on the Draft NTP Monograph on Health Effects of Low-level Lead Submitted to NTP, NIEHS, Research Triangle Park, NC

by
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Scientists at the NTP and other institutions who reviewed the extensive toxicological and epidemiological data on lead are to be commended for their efforts and careful evaluation of the scientific evidence. Overall, the conclusions are well-supported by extensive peer-reviewed scientific literature. It is a benefit to the public health community that the authors addressed complex emerging lead toxicity issues (e.g., immunonotoxicity, neurodegenerative diseases).

My comments focus on the lack of discussion of genotoxicity, which is relevant to infertility, developmental disorders, pregnancy loss, and related reproductive/developmental health. The scientific evidence on genotoxicity is extensive, benefiting greatly from assays available since the 1990s. In addition, a detailed list of human genotoxicity studies is available in the 2003 NTP "Report on Carcinogens Background Document for Lead and Lead Compounds", (http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/Lead-Public.pdf). (The appendix to this comment contains the table of human studies from this report).

Although the human studies involved blood lead levels above the targeted 10 ug/dL, genotoxicity is generally assumed to have no assumed threshold for damage (although there may be an observational threshold due to repair/deletion mechanisms). In pragmatic terms, the relevance of assays and higher exposure human studies is translated into policy in the US federal drinking water standards. These incorporate an assumption of no safe level of exposure to a genotoxic carcinogen (i.e., the Maximum Contaminant Level Goal is zero).

This is a well-established concept and suggests that both lab assay and human genotoxicity data could be mentioned, even within the low exposure scope of the report. It would be important and valuable to many readers if you provided a brief discussion of the role genotoxicity can play in reproductive and developmental toxicity. The evidence regarding sperm abnormalities is clear, with chromosome breakage reported in the single genotoxicity study cited in the report (Al Hakkak et al (1986). In addition, few scientists would argue that mutations do not pose a developmental hazard. While repair and other mechanisms may eliminate most mutations, the dynamic remains relevant. An understanding of the fact that lead is genotoxicity is as essential in this document as it was in the 2003 NTP cancer document.

I am not recommending a full analysis of the genotoxicity data, since the NTP 2003 document provides clear and substantial evidence, but do recommend that this topic be discussed briefly, with reference to the 2003 document. Thank you for consideration of this request.

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Appendix A. This table is from the NTP 2003 Report on Carcinogens Background Document for Lead and Lead Compounds, US DHHS, Research Triangle Park, NC. Citations in this table can be located at: http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/Lead-Public.pdf

End point	Results	Blood lead level[a] (µg/dL)	Exposure (country)	Reference
Chromosomal aberrations in peripheral blood lymphocytes	+	37.7	lead-exposed workers	Schwanitz *et al.* 1970[b,c] Schwanitz *et al.* 1975[b,c]
Chromosomal aberrations in peripheral blood lymphocytes	+	38 to 64	storage-battery plant workers (Italy)	Forni *et al.* 1976[b]
Chromosomal aberrations in peripheral blood lymphocytes	+	> 50	lead-exposed smelter workers (Sweden)	Nordenson *et al.* 1978[b]
Chromosomal aberrations in peripheral blood lymphocytes	+	38 to 96	storage-battery plant workers (Iraq)	Al-Hakkak *et al.* 1986[b]
Chromosomal aberrations in peripheral blood lymphocytes	+	22 to 48	storage-battery plant workers (China)	Huang *et al.* 1988[b,d]
Chromosomal aberrations (also significantly dependent on radiation dose) in peripheral blood lymphocytes	+	27.9	lead and zinc mine workers, also exposed to metals and radon (Slovenia)	Bilban 1998
Chromosomal aberrations in peripheral blood lymphocytes	+/–	40 to > 120	shipyard workers (Scotland)	O'Riordan and Evans 1974[b]
Chromosomal aberrations in peripheral blood lymphocytes	–	average 48.7	lead smelter workers (Finland)	Maki-Paakkanen *et al.* 1981[b]
Chromosomal aberrations in peripheral blood lymphocytes	–	> 30	children living near lead plant (Germany)	Bauchinger *et al.* 1977[b]
Chromosomal aberrations	–	NA	lead manufacturing industry (The Netherlands)	Schmid *et al.* 1972[b,c]
Chromosomal aberrations in peripheral blood lymphocytes	–	40	volunteers who ingested lead acetate (49 days) (The Netherlands)	Bijlsma and de France 1976[e,f]
SCE in peripheral blood lymphocytes	+	22 to 48	storage-battery plant workers (China)	Huang *et al.* 1988[b,d]
SCE in peripheral blood lymphocytes (exposure-response with blood lead levels)	+	27.9	lead and zinc mine workers, also exposed to metals and radon (Slovenia)	Bilban 1998

End point	Results	Blood lead level[a] (µg/dL)	Exposure (country)	Reference
SCE in peripheral blood lymphocytes	+	13.81	lead and zinc powder factory (Turkey)	Donmez *et al.* 1998
SCE in peripheral blood lymphocytes High-SCE-frequency cells	+ +	32.5	battery manufacturer (Taiwan)	Wu *et al.* 2002
SCE in peripheral blood lymphocytes	+/–[g]	average 48.7	lead smelter workers (Finland)	Maki-Paakkanen *et al.* 1981[b]
SCE in peripheral blood lymphocytes	+/–[h]	29 to 75	storage-battery plant workers (Denmark)	Grandjean *et al.* 1983[b]
SCE in peripheral blood lymphocytes	–	29 to 63	children living near lead smelter (Italy)	Dalpra *et al.* 1983[b]
SCE in peripheral blood lymphocytes	–	NA	battery factory workers (Mexico)	Leal-Garza *et al.* 1986[b]
SCE in peripheral blood lymphocytes	–	NR	printing-press workers (India)	Rajah and Ahuja 1995
Micronuclei in peripheral blood leukocytes	+	67.55	lead smelter workers (Bulgaria)	Vaglenov *et al.* 1997
Micronuclei in peripheral blood leukocytes	+	27.9	lead and zinc mine workers, workers also exposed to metals and radon (Slovenia)	Bilban 1998
Micronuclei in peripheral blood leukocytes	+	60.92	starter-battery plant (Slovenia)	Vaglenov *et al.* 1998
Micronuclei in blood lymphocytes	+	40	metal-powder producing workers (lead, zinc, cadmium) (Turkey)	Hamurcu *et al.* 2001
DNA-protein crosslinks in peripheral blood lymphocytes	+	32.5	battery manufacture workers (Taiwan)	Wu *et al.* 2002
DNA damage (comet assay) in peripheral blood lymphocytes significant relationship at blood levels > 27 µg/dL	+	four groups: < 13 13 to 27 27 to 37 > 37	lead smelter workers (secondary) (China)	Ye *et al.* 1999

End point	Results	Blood lead level[a] (µg/dL)	Exposure (country)	Reference
DNA damage (comet assay) in peripheral blood lymphocytes basal level sensitivity to X rays	 + +	41 to >120	battery factory workers (Colombia)	Restrepo *et al.* 2000
DNA damage (comet assay)	+	39	battery factory workers (Italy)	Fracasso *et al.* 2002
DNA repair capacity (comet assay) after exposure to X rays in peripheral blood lymphocytes	–	41 to > 120	battery factory workers (Colombia)	Restrepo *et al.* 2000
Higher mitotic activity in peripheral blood lymphocytes	+	40	volunteers who ingested lead acetate (49 days) (The Netherlands)	Bijlsma and de France 1976[b,e]
Decrease in mitotic index in peripheral blood lymphocytes	+	NR	printing press workers (India)	Rajah and Ahuja 1995
Increased mitotic activity	+	NA	lead-exposed workers (Germany)	Schwanitz *et al.* 1970[b,c]
Effects on cell division	+	NA	(not available)	Sarto *et al.* 1978[b,c]

[a]NA = not available; NR = not reported.

[b]Not reviewed in text; source: ATSDR 1999.

[c]Foreign-language publication, not reviewed here; results are those reported by ATSDR 1999.

[d]Incorrectly listed in ATSDR (1999) as environmentally exposed children and as reporting negative results for SCE; no papers by Huang and genotoxicity in environmentally exposed children were found.

[e]Incorrectly listed in ATSDR (1999) as Bulsma.

[f]Study was reviewed in ATSDR (1999) (see mitotic index), but chromosomal aberrations were not reported.

[g]SCE frequency was higher in lead-exposed smokers than in non-exposed smokers, but not higher in lead-exposed nonsmokers than control non-smokers.

[h]ATSDR (1999) also reported a slight positive correlation with duration but not level of exposure.